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Antioxidants in Cancer Treatment

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1. Introduction

There are many different chemotherapeutic agents used in cancer treatment. Most of the chemotherapeutic drugs can be divided into alkylating agents, antimetabolites, anthracyclines, plant alkaloids, topoisomerase inhibitors, and other antitumour agents. All of these drugs affect cell division or DNA synthesis and function in some way. Several classes of chemotherapy work by producing a reactive oxygen compound or free radical.

Alkylating agents work to add alkyl groups to negatively-charged groups. They are known to stop tumor growth through cross-linking guanine nucleobases in strands of DNA, which directly damages the DNA by making it unable to uncoil and separate. The cell, when attacked in this way, is unable to replicate. While it may not die, it also cannot grow. Cyclophosphamide, a cytotoxic alkylating agent, is extensively used as an antineoplastic agent for the treatment of haematological malignancies and a variety of solid tumours, including leukaemia, ovarian cancer and small-cell lung cancer. Cyclophosphamide is bioactivated by hepatic cytochrome P450 enzymes resulting in the formation of phosphoramide mustard and acrolein. The therapeutic effect of cyclophosphamide is attributed to phosphoramide mustard, while the other metabolite, acrolein is associated with toxic side effects. The cellular mechanism of cyclophosphamide toxicity is due to the production of highly reactive oxygen free radicals by these metabolites. It is obvious that high levels of ROS within the body could culminate in oxidative stress.

Anthracyclines (or anthracycline antibiotics) are a class of drugs used in cancer chemotherapy derived from Streptomyces bacteria. Anthracycline has three mechanisms of action: inhibits DNA and RNA synthesis by intercalating between base pairs of the DNA/RNA strand, thus preventing the replication of rapidly-growing cancer cells: inhibits topoiosomerase II enzyme, preventing the relaxing of supercoiled DNA and thus blocking DNA transcription and replication: creates iron-mediated free oxygen radicals that damage the DNA and cell membranes.

Radiation therapy is another type of cancer treatment that uses ionizing radiation to produce cell death through free radical formation. The cell death occurs by damaging the DNA of cancerous cells. This DNA damage is caused by one of two types of energy: photon or charged particle, directly or indirectly ionizing the atoms which make up the DNA chain. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA.

The oxidative stress produced during cancer treatment induces a range of side effects such as hair loss, nausea or vomiting and cardiotoxicity. Several authors believe that the use of antioxidants during cancer treatment can reduce these side effects. However, there is a

concern that antioxidants might reduce oxidizing free radicals created by radiotherapy and some forms of chemotherapy, and thereby decrease the effectiveness of the therapy. The authors that support the idea that administration of oral antioxidants is contraindicated during cancer therapeutics, suggest that a drug's ability to destroy micrometastases may be impaired by the addition of antioxidants and, this may result in an improved short-term tolerance to treatment followed by an increased long-term chance for recurrence. On the other hand, there are several articles showing no evidence of significant decreases in the efficacy of chemotherapy with antioxidant supplementation and that supplementation of antioxidant vitamins during cancer treatment is effective, increasing quality and life expectancy.

Considering that the use of antioxidants during treatment is a very contentious issue, the purpose of this chapter is to review studies in humans to evaluate the use of these antioxidants as a therapeutic intervention in cancer patients, and their interactions with radiation therapy and chemotherapy.

2. Classes of agents used in cancer treatment that produce a reactive oxygen compound or free radical

The ultimate clinical effectiveness of any anti-cancer drug requires that it kill malignant tumor cells *in vivo* at doses that allow enough cells in the patient's critical tissues (e.g., bone marrow, gastrointestinal tract) to survive so that recovery can occur. This is difficult to accomplish because, in general, anticancer drugs are most useful against malignant tumor with a high proportion of dividing cells, and some normal tissues such as the bone marrow and G1 tract also have a high cell-proliferation rate. Anticancer drugs used by themselves are primarily effective against high-growth-fraction tumors such as the leukemias and lymphomas. The most common malignant tumors, however, are "solid" tumors, including those of the colon, rectum, lung and breast. These tumors usually have a low proportion of dividing cells and therefore are less susceptible to treatment by drugs alone (Pratt, 1994).

There are some standard methods of cancer treaments: surgery, chemotherapy, radiation therapy, immunotherapy and biologic therapy. Undoubtedly, chemotherapy and radiotherapy are the treatments to fight cancer with more side effects.

Chemotherapy agents can be divided into several categories: alkylating agents (e.g., cyclophosphamide, ifosfamide), antibiotics which affect nucleic acids (e.g., doxorubicin, bleomycin), platinum compounds (e.g., cisplatin), mitotic inhibitors (e.g., vincristine), antimetabolites (e.g., 5-fluorouracil), camptothecin derivatives (e.g., topotecan), biological response modifiers (e.g., interferon), and hormone therapies (e.g., tamoxifen). The agents most noted for creating cellular damage by initiating free radical oxidants are the alkylating agents, the tumor antibiotics, and the platinum compounds (Lamson & Brignall, 1999).

2.1 Alkylating agents

Inhibiting DNA replication, therefore, affords a logical approach for retarding tumour growth. For this reason, DNA has become a critical target in cancer chemotherapy. Indeed, many of the antitumour agents currently in the cancer armamentarium are DNA-interactive. Among them, the DNA alkylators or cross-linkers, which include the platinum-based drugs, are the most active available for effective cancer management. By virtue of their high chemical reactivity, either intrinsic or acquired in a biological environment, all alkylating agents form covalent linkages with macromolecules having nucleophilic centres. They have

no specificity, but the chance reaction with DNA forms the basis for the antitumour effects. Bifunctional alkylating agents form covalent bonds at two nucleophilic sites on different DNA bases to induce interstrand (between two opposite strands) and/or intrastrand (on same strand) cross-links (Fig. 1). Monofunctional agents have only one alkylating group and, therefore, cannot form crosslinks (Siddik, 2002).

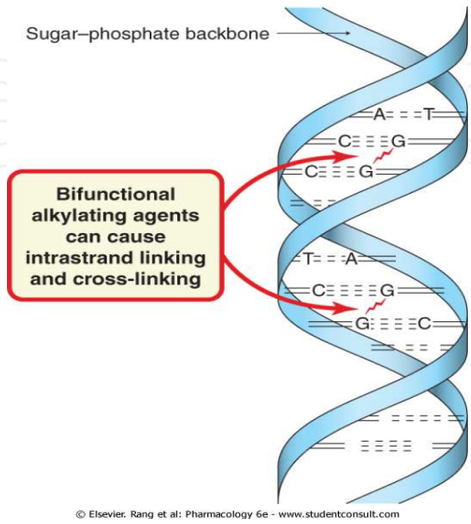

Fig. 1. The effects of bifunctional alkylating agents on DNA. Note the cross-linking of two guanines (www.studentconsult.com).

According to Siddik (2002), the end effect of these DNA-interactive agents is to inhibit DNA replication, which in turn may affect the production of RNA and protein. Such changes in the superhelical structure are then processed as distinct signals that determine whether a cell lives or dies.

The cyclophosphamide (CP) is a nitrogenous mustard pertaining to this group of substances named alkylating agents, which are effective against slow-growing tumors that damage cells at any phase of cellular growth. Cyclophosphamide is inactive per se and requires microsomal mixed function oxidase-mediated metabolism to activated metabolites capable of binding covalently to nucleic acids and proteins. The commonly accepted scheme of cyclophosphamide metabolism involves intermediate formation of 4-hydroxy-CP which undergoes ring-opening to form aldophosphamide, an isomer of 4-hydroxy-CP (Gurtoo et al., 1985). Aldophosphamide is metabolized to phosphoramide mustard and acrolein (Murgo & Weinberger, 1993).

Phosphoramide mustard forms DNA crosslinks between (interstrand crosslinkages) and within (intrastrand crosslinkages) DNA strands at guanine N-7 positions. This is irreversible and leads to cell death (Dong et al., 1995). According to Shanmugarajan et al. (2008), the therapeutic effect of cyclophosphamide is attributed to phosphoramide mustard and acrolein is associated with toxic side effects.

Adams and Klaidman (1993) showed that acrolein and its glutathione adduct, glutathionylpropionaldehyde, induce oxygen radical formation. Acrolein was oxidized by xanthine oxidase to produce acroleinyl radical and O2(.-). Aldehyde dehydrogenase metabolized acrolein to form O2.- but not acroleinyl radical. The fact that glutathionylpropionaldehyde is a more potent stimulator of oxygen radical formation than

acrolein indicates that glutathionylpropionaldehyde is a toxic metabolite of acrolein and may be responsible for some of the *in vivo* toxicity of acrolein (Adams & Klaidman, 1993). In this regard, evidences reveal that oxidative stress plays a key role in the pathogenesis of cyclophosphamide induced cardiotoxicity (Shanmugarajan et al., 2008).

2.2 Anthracyclines (antibiotics)

Anthracyclines attack cancer cells by multiple mechanisms, inhibiting replication and cells damaging in ways that promote cell death. They work primarily by DNA intercalation. In order for a cell to divide, the DNA in the cell's nucleus must be unravelled and then duplicated (a process known as transcription). Anthracyclines bind to portions of the unwound strand of nuclear DNA, halting the transcription process, which in turn prevents cell replication. Among other details, scientists have found that anthracyclines inhibit the action of topoisomerase II ("Topo II"), an enzyme that unzips the DNA molecule for replication. It is anthracycline's interference with topoisomerase II that is credited with both its cardiotoxicity and mutagenic effects, since its Topo II inhibition leaves DNA breaks at even low concentrations, resulting in an accumulation of DNA damage following prolonged, repeated, or higher exposures (Pratt, 1999).

The biological activity of several well-known and widely used anthracycline antibiotics such as daunomycin and doxorubicin is thought to be associated to the hydroxyquinone structure (Young et al., 1981). Quinones are classified by the aromatic moieties present in their structure and naphthoquinone constitutes the naphtalenic ring (Silva et al., 2003).

The naphthoquinones are a class of compounds having cytotoxic properties that can be advantageous in treating cancer. Two essential mechanisms are linked to the effects of naphthoquinone, oxidative stress and nucleophilic alkylation (Bolton et al., 2000). These substances are able to accept electrons and generate reactive oxygen species (O_2-., HO., H_2O_2), whose oxidative effects could explain the cytotoxicity produced by these compounds (Boveris et al., 1978; Silva et al., 2003; Witte et al., 2004).

Bolton et al. (2000) suggested that quinones are highly reactive molecules and can reduce the redox cycle using semi-quinine radicals, generating reactive oxygen species (ROS) that include superoxide radicals, peroxide radicals, hydrogen peroxide and hydroxyl radicals. ROS production can cause severe oxidative cell stress, forming oxidative macromolecule cells, affecting lipids, proteins and DNA.

Rajagopalan et al. (1988) demonstrated that Adriamycin, an anthracycline drug with a wide spectrum of clinical antineoplastic activity, stimulates the formation of OH in the isolated rat heart and suggests that this mechanism may be significant in Adriamycin-induced cardiotoxicity.

According to Minotti, Cairo and Monti (1999) the cardiotoxicity of anthracyclines is mediated by mechanisms that are distinct from those underlying the antitumor effects of these drugs. For these authors a major role in the development of cardiotoxicity has been assigned to iron, presumably because this metal can catalyze free radical reactions that overrule the antioxidant defenses of cardiomyocytes. For them some investigators have proposed mechanisms of cardiotoxicity that are independent altogether of both iron and free radicals. In an attempt to bridge the two extremes of this field, other studies have maintained a role for iron but not for free radicals, suggesting that anthracycline cardiotoxicity reflects disturbances in iron homeostasis within cardiomyocytes rather than the outcome of iron-catalyzed free radical injury.

2.3 Platinum compounds

The application of inorganic chemistry to medicine is a rapidly developing field, and novel therapeutic and diagnostic metal complexes are now having an impact on medical practice. Cisplatin, as one of the leading metal-based drugs, is widely used in the treatment of cancer. Significant side effects and drug resistance, however, have limited its clinical applications. Biological carriers conjugated to cisplatin analogs have improved specificity for tumor tissue, thereby reducing side effects and drug resistance (Kostova, 2006).

The history of platinum in cancer treatment began 150 years ago with the first synthesis of cisplatin, but it was not used in the clinic before 30 years ago. Then 3000 derivatives were synthesised and tested, with poor successes: three other derivatives only are available today. Clearly they are not more active, but they are less toxic than cisplatin, although two, carboplatin and nedaplatin, yield a cross-resistance, while one, oxaliplatin, does not. Their mechanisms of action are similar: these four pro-drugs form adducts with DNA, impairing DNA synthesis and repair then (Fig. 2). Their pharmacokinetics are complicated since we always measure two overlapping pharmacokinetics: those of the parent compound and of the bound platinum. Cisplatin is now recommended for few cancers, it is replaced by less-toxic carboplatin, and therefore more easily used in combination. Oxaliplatin give interesting results in a number of cancers (Desoize & Madoulet, 2002).

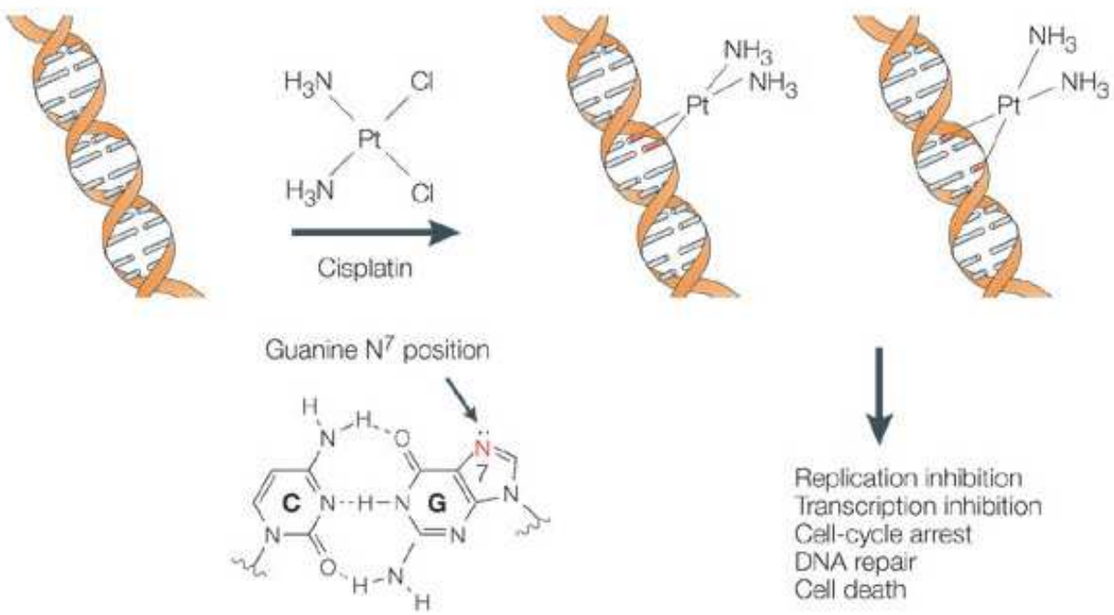

Fig. 2. The platinum atom of cisplatin binds covalently to the N7 position of purines to form 1,2- or 1,3-intrastrand crosslinks, and interstrand crosslinks. Cisplatin–DNA adducts cause various cellular responses, such as replication arrest, transcription inhibition, cell-cycle arrest, DNA repair and apoptosis (Wang & Lippard, 2005).

According to Boulikas and Vougiouka (2003) Cisplatin, carboplatin, oxaliplatin and most other platinum compounds induce damage to tumors via induction of apoptosis. Apoptosis is responsible for the characteristic nephrotoxicity, ototoxicity and most other toxicities of the drugs. The severity of cisplatin nephrotoxicity is related to platinum concentration in the kidneys. There is a growing amount of evidence that cisplatin-induced nephrotoxicity is

ascribed to oxidative damage resulting from free radical generation (Antunes & Bianchi, 2004). Reactive oxygen metabolites (superoxide, hydrogen peroxide, hydroxyl radical, and hypochlorous acid) are important mediators of renal damage in acute renal failure and glomerular and tubulointerstitial diseases (Klahr, 1997).

2.4 Radiation therapy

Radiation therapy has been used in cancer treatment for many decades. The primary focus in radiotherapy is to increase DNA damage in tumor cells, as double strand breaks are important in cell death. Another course of action is to alter cellular homeostasis, modifying signal transduction pathways, redox state, and disposition to apoptosis. The cellular changes ideally would enhance the killing of tumor cells while reducing the probability of normal cell death. Radiation damages cells by direct ionization of DNA and other cellular targets and by indirect effect through ROS. Indirect ionization happens as a result of the ionization of water, forming free radicals, notably hydroxyl radicals, which then damage the DNA (Fig. 3). Therefore, exposure to ionizing radiation produces oxygen-derived free radicals in the tissue environment; these include hydroxyl radicals (the most damaging), superoxide anion radicals and other oxidants such as hydrogen peroxide. Additional destructive radicals are formed through various chemical interactions (Borek, 2004a).

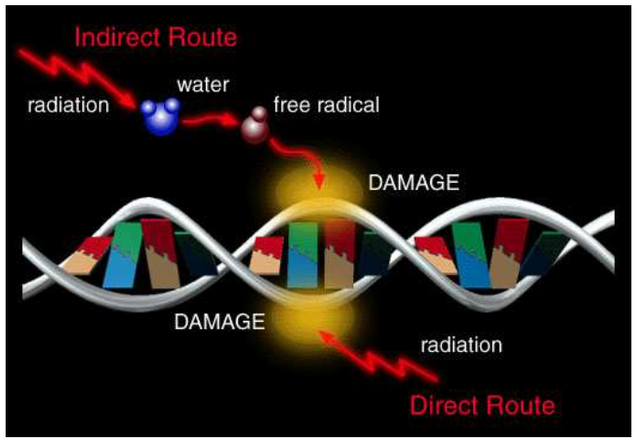

Fig. 3. There are two main ways radiation can damage DNA inside living cells. Radiation can strike the DNA molecule directly, ionizing and damaging it. Alternately, radiation can ionize water molecules, producing free radicals that react with and damage DNA molecules. Source unknown.

3. Antioxidants nutrients in cancer treatment

Cancer survivors receive a wide range of advice from many sources about foods they should eat, foods they should avoid, how they should exercise, and what types of supplements or herbal remedies they should take. Unfortunately, this advice is often conflicting (Doyle et al., 2006). Antioxidants vitamins show promise in cancer therapy by their palliative action, reducing painful side effects associated with treatment.

Examples of dietary antioxidants are vitamins A, C and E, selenium and flavonoids such as quercetin and genistein. In several *in vitro* and animal studies the hypothesis has been tested that antioxidants benefit patients receiving chemotherapy. In principle two opposing

mechanistic arguments could be advanced supporting or refuting this notion. On the one hand, antioxidants might protect cancer cells against the oxidative damage induced by chemotherapy, which would mitigate against their use. On the other hand they may enhance drug-induced cytotoxicity by blocking reactive oxidant species. (D'Incalci et al., 2007).

Antioxidants nutrients such as vitamin E, vitamin C, vitamin A, and Beta-carotene are involved in detoxification of the Reactive oxygen species (ROS). Vitamin E, A, and Beta-carotene are lipophilic antioxidants whereas vitamin C is hydrophilic antioxidant. Vitamin E function as a free radical chain breaker particularly it interferes with the propagation step of lipid peroxidation. The vitamin A and Beta-carotene have actions by quenching both singlet oxygen and other free radicals generated by photochemical reactions (Peerapatdit et al., 2006).

Simone II et al. (2007) wrote a review which showed that since the 1970s, 280 peer-reviewed *in vitro* and *in vivo* studies, including 50 human studies involving 8,521 patients, 5,081 of whom were given nutrients, have consistently shown that those non-prescription antioxidants and other nutrients do not interfere in therapeutic modalities of cancer. Furthermore, they enhance the killing of therapeutic modalities of cancer, decrease their side effects, and protect normal tissue. For them in 15 human studies, 3,738 patients who took non-prescription antioxidants and other nutrients actually had increased survival.

3.1 Vitamin A and carotenoids

Some studies show that vitamin A supplementation, during cancer treatment, shows no benefit in terms of survival (Meyskens et al., 1994; Culine et al. 1999; van Zandwijk et al., 2000). However, the term "vitamin A" commonly refers to either of two very different families of substances: retinol, or preformed vitamin A, and its synthetic analogues (retinoic acid and the carotenoids). It is important to understand that retinoids and carotenoids behave very differently in the body, each may act via a different mechanism even if they both have an anticancer effect (Hennekens et al., 1986).

A study involving a total of 18,314 smokers, former smokers, and workers exposed to asbestos evaluated the effects of a combination of 30 mg of beta carotene per day and 25,000 IU of retinol (vitamin A) in the form of retinyl palmitate per day on the primary end point, the incidence of lung cancer. After an average of four years of supplementation, the combination of beta carotene and vitamin A had no benefit and may have had an adverse effect on the incidence of lung cancer and on the risk of death from lung cancer, cardiovascular disease, and any cause in smokers and workers exposed to asbestos (Omenn et al., 1996). Other findings confirm of a lack of any benefit from administration of large doses of synthetic β-carotene in cancer prevention (Klerk et al., 1998). On the other hand the adjuvant effect of high-dose vitamin A was tested on 307 patients with stage I non-small-cell lung cancer. After curative surgery, patients were randomly assigned to either a group prescribed retinol palmitate administration (orally 300,000 IU daily for 12 months). The authors concluded that daily oral administration of high-dose vitamin A is effective in reducing the number of new primary tumors related to tobacco consumption and may improve the disease-free interval in patients curatively resected for stage I lung cancer (Pastorino et al., 1993). Antioxidants, when added adjunctively, to first-line chemotherapy, may improve the efficacy of chemotherapy and may prove to be safe (Drisko et al., 2003).

136 patients with advanced non-small cell lung cancer were randomized to receive chemotherapy (paclitaxel and carboplatin) alone or chemotherapy in combination with

ascorbic acid 6100 mg/day, dl-alpha-tocopherol (vitamin E) 1050 mg/day and beta-carotene 60 mg/day. The results do not support the concern that antioxidants might protect cancer cells from the free radical damage induced by chemotherapy (Pathak et al., 2005). The authors suggest that high-dose multiple antioxidants in conjunction with chemotherapy increase the response rates and/or survival time in advanced lung cancer.

A phase III randomized study, comparing treatment with fluorouracil, epidoxorubicin and methotrexate (FEMTX) with the best supportive care, was conducted in patients with unresectable or metastatic gastric cancer. During treatment, these patients received tablets containing vitamins A and E. This study concluded that treatment with fluorouracil, epidoxorubicin and methotrexate combined with vitamin A and E is a fairly well-tolerated treatment, giving a response rate of 29% in patients with advanced gastric cancer, and also prolonging patients' survival (Pyrhönen et al., 1995).

Alpha- and beta-carotene have been examined for *in vitro* tumor inhibitory activity against human neuroblastoma cell lines, and alpha-carotene was found to have 10 times the anti-tumor activity of beta-carotene (Murakoshi et al., 1989).

Twenty patients with advanced squamous cell carcinoma of the mouth, who received 60 Gy telecobalt therapy given in 30 daily fractions with synchronous chemotherapy comprising vincristine, methotrexate and bleomycin, were randomized to receive standard diet with supplemental beta carotene. The results reported suggest that a protective action of beta-carotene is exerted on the mucosal membrane within the radiation fields used (Mills, 1988).

Kucuk et al. (2002) conducted a clinical trial to investigate the biological and clinical effects of lycopene supplementation in patients with localized prostate cancer. Twenty-six men with newly diagnosed prostate cancer were randomly assigned to receive a tomato oleoresin extract containing 30 mg of lycopene or no supplementation for 3 weeks before radical prostatectomy. This study suggested that lycopene may have beneficial effects in prostate cancer. The authors state that preparation that was used in this study was a mixture of tomato carotenoids and other tomato phytochemicals. Although lycopene was the predominant carotenoid in the capsules, there were significant amounts of phytoene and phytofluene and other bioactive compounds. It is possible that the combination of the phytochemicals present in the tomato extract was responsible for the observed clinical effects rather than lycopene alone.

Because of the poor response of pancreatic cancer to conventional therapy Recchia et al. (1998) performed a phase II pilot study to evaluate whether beta-interferon and retinoids, added to active chemotherapeutic agents, could increase response rate and survival in a group of patients who had metastatic disease. Twenty-three chemotherapy-naive patients were treated with epirubicin, mitomycin C, and 5-fluorouracil. Beta-Interferon, 1 x 10(6) IU/m2, subcutaneously three times a week, and retinol palmitate, 50,000 IU orally twice a day, were given between chemotherapy cycles. Eight patients responded (35%) and 8 (35%) had stable disease.

Prasad et al. (1999) has reviewed several studies showing the use of vitamin A and its analogs and its importance in cancer treatment. In this review the authors present a table (Table 1) on these studies. For them vitamins A derivatives at high doses, variable extents of tumor size reduction have been reported. Retinoids have been shown to have very little or no effect on several human tumors which included melanoma, non-small cell lung carcinoma, prostate cancer, breast cancer and neuroblastoma.

Tumor type	Design	Agents	Patient no.	Response
Actinic keratoses	Phase III (randomized)	Etretinate	54	84%
Advanced squamous cell carcinoma	Phase II	13 cRA	4	50%
		13 cRA	28	80%
Mycosis fungoides	No record	13 cRA	123	60%
Laryngeal papillomatosis	Phase II	13 cRA	6	60%
Oral leukoplakia	Phase II	b-carotene (synthetic)	24	71%
	Phase III randomized	13 cRA (high dose)	44	Marked regression
Cervical cancer (CIN II or III)	Phase II	tRA (topical)	20	50%
Cervical cancer (CIN II or III)	Phase III randomized	tRA (topical)	301	Increased regression of CIN II but not CIN III
Cervical cancer (CIN II or III)	Phase II	13 cRA + INFa	23	53%
Advanced cervical cancer	Phase II	13 cRA + INFa	26	50%
Advanced cervical cancer	Phase II	13 cRA + INFa	24	30%

Data from Prasad et al. (1999).
13 cRA513-cis Retinoic acid.
INFa5Interferon a.

Table 1. Efficacy of Retinoids in the Treatment of Human Tumors

13-cis-retinoic acid, even in short-term use, appears to be an effective treatment for oral leukoplakia and has an acceptable level of toxicity. 44 patients with this disease to receive 13-cis-retinoic acid (24 patients) or placebo (20), 1 to 2 mg per kilogram of body weight per day for three months, and followed them for six months. There were major decreases in the size of the lesions in 67 percent of those given the drug and in 10 percent of those given placebo. Dysplasia was reversed in 54 percent of the drug group (Hong et al., 1986).

Some of the analogs of retinoids produce extreme toxicity. The use of single antioxidant vitamins which require very high doses for its effectiveness has no significant value in the

treatment of cancer, even though such doses may cause tumor regression of variable degrees (Prasad et al, 1999). The antitumor activity demonstrated for retinoids (especially retinoic acid) alone and in combination with other agents supports the need for targeted phase II trials to define the spectrum of responsive tumors and for laboratory studies to further delineate the biologic mechanisms associated with therapeutic responses. High priority should then be given to phase III trials to delineate optimal strategies for improving outcome by combining retinoid-based treatments with conventional chemotherapy and radiotherapy regimens (Smith et al., 1992).

Addition of nutrition supplements such as lycopene may have potential therapeutic benefit in the adjuvant management of high-grade gliomas. The results verified in fifty patients with high-grade gliomas were treated with surgery followed by adjuvant radiotherapy and concomitant paclitaxel. Patients were randomized to receive either oral lycopene 8 mg daily with radiotherapy (Puri et al., 2010).

Docetaxel is currently the most effective drug for the treatment of castration-resistant prostate cancer (CRPC), but it only extends life by an average of 2 months. Tang et al. (2011) proposed a study of the interaction between docetaxel and lycopene in CRPC models. Lycopene, an antioxidant phytochemical, has antitumor activity against prostate cancer in several models and is generally safe. In this study, the authors demonstrated that lycopene enhances the effect of docetaxel on the growth of CRPC cell lines both *in vitro* and *in vivo*. These data provide a rationale for the clinical investigation of the efficacy and safety profile of lycopene in combination with docetaxel in CRPC patients. In particular, combining lycopene with docetaxel may provide clinical benefit for men with metastatic CRPC, for whom morbidity and mortality remain high despite wide use of docetaxel chemotherapy.

3.2 Vitamin C

It has been claimed that high-dose vitamin C is beneficial in the treatment of patients with advanced cancer, especially patients who have had no prior chemotherapy. The possibility that this compound may be useful in the treatment of cancer was first raised by Cameron and Pauling (1976) that published research suggesting a survival benefit from vitamin C in cancer treatment. The results of this clinical trial were made in 100 terminal cancer patients that were given supplemental ascorbate, by intravenous infusion for 10 days and orally thereafter, as part of their routine management. This study was compared with 1000 similar patients treated identically, but who received no supplemental ascorbate. The mean survival time was more than 4.2 times as great for the ascorbate subjects (more than 210 days) as for the controls (50 days). In the same journal Cameron and Pauling (1978) published, 2 years later, additional cases, and in this paper the authors confirm the idea that patients who had ascorbate treatment benefited with enhanced quality and prolongation of life. However, in a double-blind study 100 patients with advanced colorectal cancer were randomly assigned to treatment with either high-dose vitamin C (10 g daily) (the same dose that Pauling and Cameron recommended), using oral doses only, or placebo. None had received any previous treatment with cytotoxic drugs. Vitamin C therapy showed no advantage over placebo therapy with regard to either the interval between the beginning of treatment and disease progression or patient survival (Moertel et al., 1985). Saul (2010) and González et al. (2010) contest the work of Moertel et al. (1985). For Saul (2010) it is important to note that the negative results in Moertel studies were not true replications of Cameron and Pauling's work, as A) they used oral doses only, and B) vitamin C was discontinued at the first sign of disease progression.

D'Andrea (2005) believes that the antioxidant perhaps most widely used for treating cancer is vitamin C. For the author neither study was able to show any objective improvement in disease progression or survival over placebo. However, Maciocia (2010) contest D'Andrea's conclusions. Maciocia (2010) reported that there is no evidence of significant decreases in efficacy from antioxidant supplementation during chemotherapy. For him many of the studies indicated that antioxidant supplementation resulted in either increased survival times, increased tumor responses, or both, as well as fewer toxicities than controls. He concluded that trials that assessed chemotherapy toxicities, including diarrhea, weight loss, nerve damage and low blood counts, showed that the antioxidant group suffered similar or lower rates of these side effects than the control group.

Cabanillas (2010) after trials which have included at least 1,609 patients over 33 years concluded that we still do not know whether Vitamin C has any clinically significant antitumor activity. Nor does he know which histological types of cancers, if any, are susceptible to this agent. He doesn't know with certainty which is the required plasma ascorbic acid level that will result in antitumor effects. Assuming that this level is 10 mM/L then the recommended dose of Vitamin C appears to be in the range of 1.5 g/kg three times weekly. According to Ohno et al. (2009) the administration of more than 10 g of ascorbate is proposed to achieve plasma concentrations of 1 to 5 mM. At this time, vitamin C at high plasma concentration may function as a pro-oxidant. This occurs in the presence of free transition metals, such as copper and iron, which are reduced by ascorbate and, in turn, react with hydrogen peroxide (H2O2), leading to the formation of highly reactive and damaging hydroxyl radicals. As normal tissue receives adequate blood flow and is rich in antioxidant enzymes (e.g. catalase, glutathione peroxidase) in the blood, any H2O2 formed will be immediately destroyed. Meanwhile, tumor tissue is often associated with reduced blood flow and antioxidant enzymes, and consequently formed H2O2 remains active leading to cell damage and death. González et al. (2010) says that doses of 50-100 g given intravenously may result in plasma concentrations of about 14,000 micromol/L. At concentrations above 1000 micromol/L, vitamin C is toxic to cancer cells but not to normal cells *in vitro*. However, it is important that when referring to the plasma concentrations necessary to achieve antineoplastic activity there are other numerous factors involved that will affect the specific response. Some of these include sensitivity of tumor, hypoxia inducible factor, intracellular Redox signal transduction and gene expression, apoptosis, autoschizis, effect of collagen on tumor encapsulation and others.

Simone II et al. (2007) affirms that antioxidants and other nutrients do not interfere with cancer therapeutic modalities, enhance their killing capabilities, decrease their side effects, or protect normal tissues, and in 15 human studies, 3,738 patients actually had prolonged survival. Antioxidant and other nutrient food supplements are safe and can help to enhance cancer patient care.

Adriamycin (ADR) is effective against a wide range of human neoplasms. However, its clinical use is compromised by serious cardiac toxicity, possibly through induction of peroxidation in cardiac lipids. Ascorbic acid, a potent antioxidant, was examined for effect in reducing ADR toxicity in mice and guinea pigs. Ascorbic acid had no effect on the antitumor activity of ADR in mice inoculated with leukemia L1210 or Ehrlich ascites carcinoma, but it significantly prolonged the life of animals treated with ADR. The significant prevention of ADR-induced cardiomyopathy in guinea pigs by ascorbic acid was proved by electron microscopy. Ascorbic acid and the derivatives may delay general toxicity of ADR and also prevent the cardiac toxicity (Shimpo et al., 1991).

Borek (2004a) says in his studies that the antioxidants do protect against radiation-induced oncogenic transformation in experimental systems. However, she does not have comparable human studies that show the same association. Antioxidants do reduce the painful side effects of radiation therapy, thus supporting the beneficial effects of antioxidants in protecting normal cells in radiation therapy and in being used in conjunction with treatment for certain cancers. When considering antioxidant supplementation during treatment, it is doubtful whether high doses of radiation given in certain treatments would be rendered less effective if patients took a daily supplement of antioxidants.

Twenty consecutive symptomatic outpatients with endoscopically documented radiation proctitis seen in a single gastroenterology clinic were given a combination of vitamin E (400 IU tid) and vitamin C (500 mg tid). These patients presented with one or more of the following symptoms: rectal bleeding, rectal pain, diarrhea, or fecal urgency. There was a significant ($p < 0.05$; Wilcoxon rank) improvement in the symptom index (before treatment vs after treatment with vitamins E and C) for bleeding, diarrhea, and urgency. Patients with rectal pain did not improve significantly. Bleeding resolved in four of 11 patients, diarrhea resolved in eight of 16 patients, fecal urgency resolved in three of 16 patients, and rectal pain resolved in two of six patients. Lifestyle improved in 13 patients, including seven patients who reported a return to normal (Kennedy et al., 2001).

Cancer treatment by radiation and anticancer drugs reduces inherent antioxidants and induces oxidative stress, which increases with disease progression. Vitamins E and C have been shown to ameliorate adverse side effects associated with free radical damage to normal cells in cancer therapy, such as mucositis and fibrosis, and to reduce the recurrence of breast cancer. While clinical studies on the effect of anti-oxidants in modulating cancer treatment are limited in number and size, experimental studies show that antioxidant vitamins and some phytochemicals selectively induce apoptosis in cancer cells but not in normal cells and prevent angiogenesis and metastatic spread, suggesting a potential role for antioxidants as adjuvants in cancer therapy (Borek, 2004b).

3.3 Vitamin E

Vitamin E comprises a group of compounds possessing vitamin E activity. alpha-Tocopherol is the compound demonstrating the highest vitamin E activity, which is available both in its natural form as RRR-alpha-tocopherol isolated from plant sources, but more common as synthetically manufactured all-rac-alpha-tocopherol. Synthetic all-rac-alpha-tocopherol consists of a racemic mixture of all eight possible stereoisomers (Jensen & Lauridsen, 2007).

The ability of the vitamin E (RRR-α-tocopherol) derivatives α-tocopheryl succinate (α-TOS) and α-tocopheryloxyacetic acid (α-TEA) to suppress tumor growth in preclinical animal models has recently led to increased interest in their potential use for treating human cancer (Hahn et al., 2006).

With aim to evaluate the neuroprotective effect of antioxidant supplementation with vitamin E in patients treated with cisplatin chemotherapy Pace et al. (2003) evaluated, between April 1999 and October 2000, forty-seven patients assigned to either group one, which received vitamin E supplementation during cisplatin chemotherapy, or to group two, which received cisplatin chemotherapy alone. Alpha-tocopherol (vitamin E; 300 mg/d) was administered orally before cisplatin chemotherapy and continued for 3 months after the treatment suspension. The severity of neurotoxicity, measured with a comprehensive

neurotoxicity score based on clinical and neurophysiological parameters, was significantly lower in patients who were supplemented with vitamin E than in patients who were not supplemented with vitamin E. Thirty-one patients with cancer treated with six courses of cumulative cisplatin, paclitaxel, or their combination regimens were randomly assigned in two groups and followed by neurologic examination and electrophysiologic study. Patients assigned in Group I (n = 16) received oral vitamin E at a daily dose of 600 mg/day during chemotherapy and 3 months after its cessation were compared to patients of Group II (n = 15), who received no supplementation and served as controls. This study showed significantly that the vitamin E supplementation in cancer patients may have an important neuroprotective effect (Argyriou et al., 2005). Contradicting the idea of these authors, Kottschade et al. (2010) published new data where two-hundred seven patients were enrolled between December 1, 2006 and December 14, 2007, producing 189 evaluable cases for analysis. A phase III, randomized, double-blind, placebo-controlled study was conducted in patients undergoing therapy with neurotoxic chemotherapy (cytotoxic agents included: taxanes, cisplatin, carboplatin, oxaliplatin, or combination), utilizing twice daily dosing of vitamin E (400 mg)/placebo. The authors concluded that Vitamin E did not appear to reduce the incidence of sensory neuropathy in the studied group of patients receiving neurotoxic chemotherapy.

Prasad et al. (2003) showed in their review article that alpha-Tocopheryl Succinate is the most Effective Form of Vitamin E for Adjuvant Cancer Treatment. For them alpha-Tocopheryl Succinate inhibits the proliferation of rodent and human cancer cells without affecting the proliferation of most normal cells. In addition, they also show that alpha-Tocopheryl Succinate when used in combination with some standard and experimental cancer therapeutic agents may enhance their growth-inhibitory effect on cancer cells, while protecting normal cells against some of their toxicities.

Chemotherapy- and radiotherapy-induced oral mucositis represents a therapeutic challenge frequently encountered in cancer patients. This side effect causes significant morbidity and may delay the treatment plan, as well as increase therapeutic expenses (Köstler et al., 2001). A randomized, double-blind, placebo-controlled study was performed to evaluate the efficacy of topical vitamin E in the treatment of oral mucositis in patients receiving chemotherapy for various types of malignancy. A total of 18 patients, 17 of whom had solid tumors and one with acute leukemia, were included in this study. Lesions were observed daily prior to and 5 days after topical application of either vitamin E or placebo oil. Six of nine patients receiving vitamin E had complete resolution of their oral lesions. In eight of nine patients who received placebo, complete resolution of their oral lesions was not observed. This difference is statistically significant ($p = 0.025$ by Fisher's exact test). No toxicity was observed in this study. These results suggest that vitamin E may be an effective therapy in patients with chemotherapy-induced mucositis (Wadleigh et al., 1992).

Women with breast carcinoma were asked to complete a questionnaire that recorded their use of dietary supplements. Blood samples were obtained for the assessment of serum vitamin B12 and folate levels before and after the first cycle of chemotherapy and for weekly complete blood counts. Toxicity was evaluated by measuring absolute neutrophil counts and the frequency and severity of oral mucositis. Of the 49 women who submitted questionnaires, 35 (71%) took a combined total of 165 supplements. The decrease in neutrophil count caused by chemotherapy was ameliorated by dietary supplementation with a multivitamin or vitamin E. However, neither multivitamin use nor vitamin E use appeared to be associated with the severity of mucositis. (Branda et al., 2004).

Conditioning therapy preceding bone marrow transplantation usually consists of high-dose chemotherapy and total body irradiation. It has acute and delayed toxic effects on several tissues, possibly related to peroxidation processes and exhaustion of antioxidants (Clemens et al., 1997). Blood from 19 patients was examined for the essential antioxidants alpha-tocopherol and beta-carotene before, during, and after bone marrow transplantation (BMT). Marrow ablation and immunosuppression for BMT conditioning was achieved by treatment with high-dose chemotherapy, mostly combined with total body irradiation. All patients required total parenteral nutrition beginning 1 wk before BMT. After conditioning therapy the concentration of absolute and lipid- standardized alpha-tocopherol and beta-carotene in plasma decreased significantly, presumably as a result of an enhanced breakdown of these antioxidants. The loss of these lipid-soluble antioxidants has to be considered as a possible cause for early posttransplant organ toxicity (Clemens et al., 1990). Therefore, the antioxidant supplementation prior to conditioning therapy reduces peroxidation processes induced by conditioning therapy in bone marrow recipients.

In the Women's Health Study conducted between 1992 and 2004, 39 876 apparently healthy US women aged at least 45 years were randomly assigned to receive vitamin E or placebo and aspirin or placebo, using a 2 × 2 factorial design, and were followed up for an average of 10.1 years (Lee et al., 2005). The data from this large trial indicated that 600 IU of natural-source vitamin E taken every other day provided no overall benefit for major cardiovascular events or cancer, did not affect total mortality, and decreased cardiovascular mortality in healthy women. Therefore, these data do not support recommending vitamin E supplementation for cardiovascular disease or cancer prevention among healthy women.

On the other hand, Nechuta et al. (2011) conducted a population-based prospective cohort study of 4,877 women aged 20 to 75 years diagnosed with invasive breast cancer in Shanghai, China, between March 2002 and April 2006. Women were interviewed approximately 6 months after diagnosis and followed up by in-person interviews and record linkage with the vital statistics registry. Women who used antioxidants (vitamin E, vitamin C, multivitamins) had 18% reduced mortality risk and 22% reduced recurrence risk. Therefore, Vitamin supplement use in the first 6 months after breast cancer diagnosis may be associated with reduced risk of mortality and recurrence.

Bladder cancer is one of the most aggressive epithelial tumors characterized by a high rate of early systemic dissemination. Patients with metastatic bladder cancer are routinely treated with systemic chemotherapy such as methotrexate, vinblastine, doxorubicin, and cisplatin regimen, particularly in the setting of unresectable, diffusely metastatic, measurable disease. In a study was investigated the cytotoxic effect of vitamin E succinate (α-TOS) and the enhancement of chemosensitivity to paclitaxel by α-TOS in bladder cancer. KU-19-19 and 5637 bladder cancer cell lines were cultured in α-TOS and/or paclitaxel *in vitro*. For *in vivo* therapeutic experiments, pre-established KU-19-19 tumors were treated with α-TOS and/or paclitaxel. The results demonstrated the efficacy and therapeutic potential of α-TOS and its enhancement of chemosensitivity to paclitaxel in bladder cancer cells. α-TOS inhibits NF-κB activity resulting in the promotion of apoptotic mechanisms in bladder cancer cell lines and also reduces activated NF-κB induced by paclitaxel resulting in enhanced apoptosis *in vitro*.α-TOS displayed an antitumor effect and α-TOS in combination with paclitaxel demonstrated dramatic tumor inhibition in an *in vivo* s.c. KU-19-19 tumor model (Kanai et al., 2010). For these authors additional studies are needed to confirm its safety for use in clinical trials, the cytotoxic effect of α-TOS and its enhancement of paclitaxel treatment might provide a novel strategy for advanced or metastatic bladder cancer patients.

3.4 Selenium

Selenium was recognized as a nutritional essential only in the late 1950s. That it might also be anticarcinogenic was first suggested a decade later based on ecological relationships of cancer mortality rates and forage crop selenium contents in the United States. Since that time, a substantial body of scientific evidence indicated that selenium can, indeed, play a role in cancer prevention. This is supported by a remarkably consistent body of findings from studies with animal tumor and cell culture models, and by some, but not all epidemiologic observations (Combs Jr., 2005). Selenium is an essential element that is specifically incorporated as selenocystein into selenoproteins. It is a potent modulator of eukaryotic cell growth with strictly concentration-dependant effects. Lower concentrations are necessary for cell survival and growth, whereas higher concentrations inhibit growth and induce cell death (Selenius et al., 2010). The protective effect of this mineral is especially associated with its presence in glutathione peroxidase and thioredoxin reductase, enzymes that protect the DNA and other cellular components against oxidative damage caused by ROS. Several studies have demonstrated reduced expression of these enzymes in various types of cancer, especially when associated with a low intake of selenium, which may exacerbate the damage (Almondes et al., 2010).

A total of 1312 patients (mean age, 63 years; range, 18-80 years) with a history of basal cell or squamous cell carcinomas of the skin were randomized from 1983 through 1991. Patients were treated for a mean (SD) of 4.5 (2.8) years and had a total follow-up of 6.4 (2.0) years. The patients were treated with oral administration of 200 µg of selenium per day or placebo. After a total follow-up of 8271 person-years, selenium treatment did not significantly affect the incidence of basal cell or squamous cell skin cancer. Therefore, Selenium treatment did not protect against development of basal or squamous cell carcinomas of the skin. However, results from secondary end-point analyses support the hypothesis that supplemental selenium may reduce the incidence of, and mortality from, carcinomas of several sites (Clark et al., 1996). Selenium treatment was associated with a significant (63%) reduction in the secondary endpoint of prostate cancer incidence during 1983-93 (Clark et al., 1998). A total of 974 men with a history of either a basal cell or squamous cell carcinoma were randomized to either a daily supplement of 200 microg of selenium or a placebo. Supplementation with a nutritional dose of the essential trace element selenium significantly reduced the incidence of prostate cancer in a population of patients with non-melanoma skin cancer. For the authors this was the first completed double-blind randomized controlled trial to specifically test if a dietary supplement can prevent prostate cancer. These results require confirmation in independent trials, but suggest that selenium supplementation may be important for both the primary and secondary prevention of prostate cancer.

A prospective study included 209 breast cancer patients treated by external beam radiotherapy from December 2007 until August 2008. Plasma selenium concentrations were determined before and at the end of the radiotherapeutic treatment. Sixty patients (28.7%) were in clinical stage I, 141 (67.5%) in clinical stage II and 8 (3.8%) in clinical stage III. At the beginning of radiotherapy, the mean selenium value for all patients was 86.4 µg/l and after radiation this value dropped to 47.8 µg/l. Multivariate analysis showed statistically significant difference in the plasma selenium concentration before and after radiotherapy. Therefore, significant reduction in plasma levels of selenium is recorded in patients undergoing radiotherapy, suggesting attention to the nutritional status of this micronutrient and other antioxidant agents (Franca et al., 2010).

However, a phase 2 randomized, double-blind, placebo-controlled clinical trial was conducted in men with localized nonmetastatic prostate cancer who had elected to forgo active treatment and be followed by active surveillance. A total of 140 men were randomized to placebo (n = 46), 200 µg/d (n = 47), or 800 µg/d (n = 47) selenium p.o. (as selenized yeast) and followed every 3 months for up to 5 years. Prostate-specific antigen (PSA) velocity was used as a marker of prostate cancer progression and was estimated using mixed-effects regression. Selenium supplementation did not show a protective effect on PSA velocity in subjects with localized prostate cancer. On the contrary, supplementation with high-dose selenium was observed to be a risk factor for increased PSA velocity in men with high baseline plasma selenium concentrations (Stratton et al., 2010).

3.5 Flavonoids

Flavonoids and their polymers constitute a large class of food constituents, synthesized by plants, many of which alter metabolic processes and have a positive impact on health. Flavonoids are a subclass of polyphenols (Beecher, 2003). Polyphenols are abundant micronutrients in our diet, and evidence for their role in the prevention of degenerative diseases such as cancer and cardiovascular diseases is emerging. The health effects of polyphenols depend on the amount consumed and on their bioavailability (Manach et al., 2004). The capacity of flavonoids to act as antioxidants *in vitro* has been the subject of several studies in the past years, and important structure−activity relationships of the antioxidant activity have been established. The antioxidant efficacy of flavonoids *in vivo* is less documented, presumably because of the limited knowledge on their uptake in humans (Pietta, 2000).

Sadzuka et al. (1998) investigated the effects of green tea and tea components on the antitumor activity of doxorubicin. We carried out the combined treatment of doxorubicin and green tea on Ehrlich ascites carcinoma tumor-bearing mice. The oral administration of green tea enhanced 2.5-fold the inhibitory effects of doxorubicin on tumor growth. The doxorubicin concentration in the tumor was increased by the combination of green tea with doxorubicin. In contrast, the increase in doxorubicin concentration was not observed in normal tissues after green tea combination. Furthermore, the enhancement of antitumor activity of doxorubicin induced by green tea was observed in M5076 ovarian sarcoma, which has low sensitivity to doxorubicin. These results suggest that drinking green tea can encourage cancer chemotherapy and may improve the quality of life of clinical patients.

A study demonstrates, for the first time, that cancer preventive effects of epigallocatechin gallate (EGCG) and quercetin can inhibit the self-renewal capacity of prostate cancer stem cells. In this study Tang et al. (2010) present data indicating that human prostate cancer cell lines contain a small population of CD44+CD133+ cancer stem cells and their self-renewal capacity is inhibited by EGCG. Furthermore, EGCG inhibits the self-renewal capacity of CD44+a2b1+CD133+ CSCs isolated from human primary prostate tumors, as measured by spheroid formation in suspension. EGCG induces apoptosis by activating capase-3/7 and inhibiting the expression of Bcl-2, survivin and XIAP in CSCs. Furthermore, EGCG inhibits epithelial-mesenchymal transition by inhibiting the expression of vimentin, slug, snail and nuclear b-catenin, and the activity of LEF-1/TCF responsive reporter, and also retards CSC's migration and invasion, suggesting the blockade of signaling involved in early metastasis. Interestingly, quercetin synergizes with EGCG in inhibiting the self-renewal properties of prostate CSCs, inducing apoptosis, and blocking CSC's migration and invasion. These data suggest that EGCG either alone or in combination with quercetin can eliminate cancer stem cell-characteristics.

Resistance of cancer cells to multiple chemotherapeutic drugs (a mechanism termed MDR) is a major obstacle to the success of cancer chemotherapy and has been closely associated with treatment failure. One of the most studied mechanisms of drug resistance is characterized by a decrease in drug accumulation resulting from over-expression of the 170 kDa plasma membrane, P-glycoprotein (Pgp). P-glycoprotein (Pgp), causes the efflux of chemotherapeutic drugs from cells and is believed to be an important mechanism in multidrug resistance (MDR) in human cancer (Khantamat et al., 2004). Khantamat et al. (2004) demonstrated that the flavonoid, i.e. kaempferol, could reverse the vinblastine resistant phenotype by inhibiting Pgp activity in KB-V1 cells, and the ability to affect the Pgp activity could be of relevance to the chemosensitization of this flavonoid towards anticancer drugs.

3.6 Melatonin

Melatonin, a derivative of an essential amino acid, tryptophan, was first identified in bovine pineal tissue and subsequently it has been portrayed exclusively as a hormone. Recently accumulated evidence has challenged this concept. Melatonin is present in the earliest life forms and is found in all organisms including bacteria, algae, fungi, plants, insects, and vertebrates including humans. Several characteristics of melatonin distinguish it from a classic hormone such as its direct, non-receptor-mediated free radical scavenging activity. As melatonin is also ingested in foodstuffs such as vegetables, fruits, rice, wheat and herbal medicines, from the nutritional point of view, melatonin can also be classified as a vitamin. It seems likely that melatonin initially evolved as an antioxidant, becoming a vitamin in the food chain, and in multicellular organisms (Tan et al., 2003).

Melatonin was found to be a potent free radical scavenger in 1993, since then over 800 publications have directly or indirectly confirmed this observation. Melatonin scavenges a variety of reactive oxygen and nitrogen species including hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide and peroxynitrite anion. The mechanisms of melatonin's interaction with reactive species probably involves donation of an electron to form the melatoninyl cation radical or through an radical addition at the site C3. Other possibilities include hydrogen donation from the nitrogen atom or substitution at position C2, C4 and C7 and nitrosation. Melatonin also has the ability to repair damaged biomolecules as shown by the fact that it converts the guanosine radical to guanosine by electron transfer. Unlike the classical antioxidants, melatonin is devoid of prooxidative activity and all known intermediates generated by the interaction of melatonin with reactive species are also free radical scavengers. This phenomenon is defined as the free radical scavenging cascade reaction of the melatonin family. Due to this cascade, one melatonin molecule has the potential to scavenge up to 4 or more reactive species. This makes melatonin very effective as an antioxidant. Under in vivo conditions, melatonin is often several times more potent than vitamin C and E in protecting tissues from oxidative injury when compared at an equivalent dosage (mmol / kg) (Tan et al., 2002).

Physiologic and pharmacologic concentrations of the pineal hormone melatonin have shown chemopreventive, oncostatic, and tumor inhibitory effects in a variety of in vitro and in vivo experimental models of neoplasia. Multiple mechanisms have been suggested for the biological effects of melatonin. Not only does melatonin seem to control development alone but also has the potential to increase the efficacy and decrease the side effects of chemotherapy when used in adjuvant settings (Jung & Ahmad, 2006).

Melatonin has a variety of functions in human physiology and is involved in a number of pathological events including neoplastic processes. The tissue protective actions of

melatonin are attributed to its antioxidant activity though, under certain conditions, melatonin might also exert oxidant effects, particularly in cancer cells. Büyükavcı et al. (2006) verified that these pro-oxidant actions of melatonin may assist in limiting leukemic cell growth. A similar study (Bejarano et al., 2011) evaluated the pro-oxidant effects of melatonin in tumour cell lines of human haematopoietic origin. Melatonin treatment was able to stimulate production of intracellular reactive oxygen species (ROS), as revealed by the increase in rhodamine-123 fluorescence, which was associated with significant cytotoxicity and activation of caspase activities. According to authors, this pro-oxidant action of melatonin may assist in limiting tumour cell growth. An increase in the activation of caspase-3, -8, -9 was also observed when melatonin was combined with vincristine in Ewing sarcoma cell line (Casado-Zapico et al., 2010).

A study was done with 14 women with metastatic breast cancer who did not respond to tamoxifen (TMX) therapy or progressed after initial disease stabilization. The study evaluated the biological and clinical effects of a concomitant melatonin therapy in women with metastatic breast cancer who had progressed in response to TMX alone. Melatonin was given orally at 20 mg day in the evening, every day starting 7 days before TMX, which was given orally at 20 mg day at noon. The authors concluded that this preliminary phase II study would suggest that the pineal hormone melatonin may amplify the therapeutic efficacy of TMX in women with metastatic breast cancer and induce objective tumour regressions in patients who have not responded to previous therapy with TMX alone (Lissoni et al., 1995).

A study included 70 consecutive advanced non-small cell lung cancer patients (NSCLC), with poor clinical status, were randomized to receive chemotherapy alone with cisplatin (20 mg/m2/day i.v. for 3 days) and etoposide (100 mg/m2/day i.v. for 3 days) or chemotherapy plus melatonin (20 mg/day orally in the evening). Cycles were repeated at 21-day intervals. Clinical response and toxicity were evaluated according to World Health Organization criteria. The percent of 1-year survival was significantly higher in patients treated with melatonin plus chemotherapy than in those who received chemotherapy alone. Finally, chemotherapy was well tolerated in patients receiving melatonin, and in particular the frequency of myelosuppression, neuropathy, and cachexia was significantly lower in the melatonin group. This study shows that the concomitant administration of melatonin may improve the efficacy of chemotherapy, mainly in terms of survival time, and reduce chemotherapeutic toxicity in advanced NSCLC, at least in patients in poor clinical condition (Lissoni et al., 1997).

Lissoni et al. (1999) evaluated effects of concomitant melatonin administration on toxicity and efficacy of several chemotherapeutic combinations in advanced cancer patients with poor clinical status. The study included 250 metastatic solid tumour patients (lung cancer, 104; breast cancer, 77; gastrointestinal tract neoplasms, 42; head and neck cancers, 27), who were randomized to receive melatonin (20mg/day orally every day) plus chemotherapy, or chemotherapy alone. Chemotherapy consisted of cisplatin (CDDP) plus etoposide or gemcitabine alone for lung cancer, doxorubicin alone, mitoxantrone alone or paclitaxel alone for breast cancer, 5-FU plus folinic acid for gastro-intestinal tumours and 5-FU plus CDDP for head and neck cancers. The 1-year survival rate and the objective tumour regression rate were significantly higher in patients concomitantly treated with melatonin than in those who received chemotherapy alone. The concomitant administration of melatonin significantly reduced the frequency of thrombocytopenia, neurotoxicity, cardiotoxicity, stomatitis and asthenia. This study indicates that the pineal hormone melatonin may

enhance the efficacy of chemotherapy and reduce its toxicity, at least in advanced cancer patients of poor clinical status.
A clinical trial was performed in locally advanced or metastatic patients with solid tumours other than renal cell cancer and melanoma. The study included 80 consecutive patients, who were randomized to be treated with interleukin 2 (IL-2) alone subcutaneously (3 million IU day-1 at 8.00 p.m. 6 days a week for 4 weeks) or IL-2 plus melatonin (40 mg day-1 orally at 8.00 p.m. every day starting 7 days before IL-2). Tumour objective regression rate was significantly higher in patients treated with IL-2 and melatonin than in those receiving IL-2 alone. The mean increase in lymphocyte and eosinophil number was significantly higher in the IL-2 plus melatonin group than in patients treated with IL-2 alone; on the contrary, the mean increase in the specific marker of macrophage activation neopterin was significantly higher in patients treated with IL-2 alone. The treatment was well tolerated in both groups of patients. This study shows that the concomitant administration of the pineal hormone melatonin may increase the efficacy of low-dose IL-2 subcutaneous therapy (Lissoni et al., 1994).

3.7 Dexrazoxane

Dexrazoxane received FDA approval in 1995 for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m2 and who continue to receive doxorubicin therapy. For this use, dexrazoxane is given immediately before doxorubicin i.v. in a ratio (in milligrams) of 10:1 dexrazoxane: doxorubicin. In Europe, a 20:1 ratio is used. Thus, in Europe, a typical schedule for cardioprotection in a patient receiving 50 mg/m2 of doxorubicin includes a single dose of 1,000 mg/m2 of dexrazoxane given immediately prior to doxorubicin. From this experience, the sponsor selected the 3-day schedule used in the clinical studies. Renal excretion of dexrazoxane is substantial; based on a model of systemic exposure, the dose should be reduced by 50% in patients with creatinine clearance values <40 ml/minute. The possible benefit of alternative dose schedules has not been examined. The sponsor is conducting a population pharmacokinetic analysis to compare population parameter estimates and interindividual variability with literature values for dexrazoxane. There are no known drug interactions (Kane et al., 2008).
It has been proposed that dexrazoxane may act through its rings-opened hydrolysis product ADR-925, which can either remove iron from the iron-doxorubicin complex or bind to free iron, thus preventing iron-based oxygen radical formation. However, it is not known whether the antioxidant actions of dexrazoxane are totally dependent on its metabolization to its rings-opened hydrolysis product and whether dexrazoxane has any effect on the iron-independent oxygen free radical production. However, Junjing et al. (2010) demonstrated that dexrazoxane was an antioxidant that could effectively scavenge these free radicals and the scavenging effects of dexrazoxane did not require the enzymatic hydrolysis. In addition, dexrazoxane was capable to inhibit the generation superoxide and hydroxyl radicals in iron free reaction system, indicating that the antioxidant properties of dexrazoxane were not solely dependent on iron chelation. Thus the application of dexrazoxane should not be limited to doxorubicin-induced cardiotoxicity. Instead, as an effective antioxidant that has been clinically proven safe, dexrazoxane may be used in a broader spectrum of diseases that are known to be benefited by antioxidant treatments.

Between January, 1996, and September, 2000, children with high-risk acute lymphoblastic leukaemia (ALL) were enrolled from nine centres in the USA, Canada, and Puerto Rico. Patients were assigned by block randomisation to receive ten doses of 30 mg/m2 doxorubicin alone or the same dose of doxorubicin preceded by 300 mg/m2 dexrazoxane. In this study was established the long-term effect of dexrazoxane on the subclinical state of cardiac health in survivors of childhood high-risk ALL 5 years after completion of doxorubicin treatment. 100 children were assigned to doxorubicin (66 analysed) and 105 to doxorubicin plus dexrazoxane (68 analysed). 5 years after the completion of doxorubicin chemotherapy, mean left ventricular fractional shortening and end-systolic dimension Z scores were significantly worse than normal for children who received doxorubicin alone but not for those who also received dexrazoxane. The protective effect of dexrazoxane, relative to doxorubicin alone, on left ventricular wall thickness and thickness-to-dimension ratio were the only statistically significant characteristics at 5 years. Subgroup analysis showed dexrazoxane protection for left ventricular fractional shortening at 5 years in girls, but not in boys. Similarly, subgroup analysis showed dexrazoxane protection for the left ventricular thickness-to-dimension ratio at 5 years in girls, but not in boys. With a median follow-up for recurrence and death of 8·7 years, event-free survival was 77% for children in the doxorubicin-alone group, and 76% for children in the doxorubicin plus dexrazoxane group (Lipshultz et al., 2010). The authors concluded that dexrazoxane provides long-term cardioprotection without compromising oncological efficacy in doxorubicin-treated children with high-risk ALL. Dexrazoxane exerts greater long-term cardioprotective effects in girls than in boys.

Lopez et al. (1998) conducted a randomized trial to evaluate primarily the cardioprotective effect of dexrazoxane in patients with advanced breast cancer and soft tissue sarcomas treated with high-dose epirubicin. Patients with breast cancer (n = 95) or STS (n = 34) received epirubicin 160 mg/m2 by intravenous (I.V.) bolus every 3 weeks with or without dexrazoxane 1,000 mg/m2 I.V. In either disease, antitumor response rates, time to progression, and survival did not significantly differ between the two arms. There was little difference in noncardiac toxicity for the two treatment groups. All methods of cardiac evaluation clearly documented the cardioprotective effect of dexrazoxane. Dexrazoxane significantly protects against the development of cardiotoxicity when high single doses of epirubicin are used. Apparently, there was no evidence of an adverse impact of dexrazoxane on antitumor activity.

Choi et al. (2010) enrolled patients who were diagnosed as having solid tumors and treated them with the same chemotherapeutic regimen. Doxorubicin was administered at a dose of 30 mg/m^2 in combination with cisplatin 60 mg/m^2, cyclophosphamide 60 mg/kg, and etoposide 200 mg/m^2 at intervals of 4 weeks with or without chest radiation therapy. Doxorubicin was administered intravenously as a bolus infusion. Dexrazoxane was administered intravenously 30 min prior to each dose of doxorubicin in the 10:1 ratio dexrazoxane: doxorubicin. There was no clinically significant side effect associated with dexrazoxane administration. The authors concluded that dexrazoxane reduces the incidence and severity of early and late cardiotoxicity in children with solid tumors receiving doxorubicin chemotherapy. Administration of dexrazoxane was well tolerated and no second malignant neoplasm was observed during the follow-up period, which might be contributed by the limited follow-up period. For them, this study supports the benefit of dexrazoxane as a cardioprotective agent in children who are vulnerable to cardiac damage by anthracycline.

4. Conclusion

Until the present moment studies have shown that the association of antioxidant vitamins for the treatment of cancer is still a controversial issue. However, with few exceptions, we can say that most studies have reported positive findings from the interaction of antioxidants during cancer treatment. The majority of conventional chemotherapeutic agents cause cell death by directly inhibiting the synthesis of DNA or interfering with its function. Adverse effects such as cardiotoxicity of many drugs in cancer treatment are mediated by mechanisms that are distinct from those underlying the antitumor effects of these drugs. Most agents do not really depend that much on free radical damaging mechanisms of action. Thus, free radical generation would arise with an adverse effect and not as a primary mechanism of action. Although further studies are needed, the predominance of evidence supports a provisional conclusion that dietary antioxidants do not conflict with the use of chemotherapy in the treatment of a wide variety of cancers and may significantly mitigate the adverse effects of that treatment.

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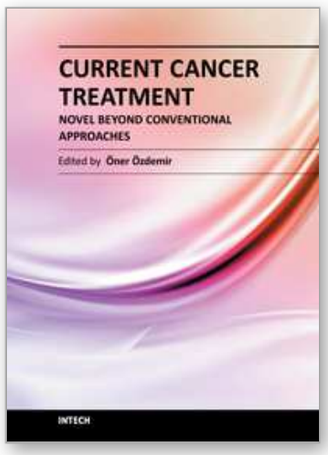

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Currently there have been many armamentaria to be used in cancer treatment. This indeed indicates that the final treatment has not yet been found. It seems this will take a long period of time to achieve. Thus, cancer treatment in general still seems to need new and more effective approaches. The book "Current Cancer Treatment - Novel Beyond Conventional Approaches", consisting of 33 chapters, will help get us physicians as well as patients enlightened with new research and developments in this area. This book is a valuable contribution to this area mentioning various modalities in cancer treatment such as some rare classic treatment approaches: treatment of metastatic liver disease of colorectal origin, radiation treatment of skull and spine chordoma, changing the face of adjuvant therapy for early breast cancer; new therapeutic approaches of old techniques: laser-driven radiation therapy, laser photo-chemotherapy, new approaches targeting androgen receptor and many more emerging techniques.

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